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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/047,352	01/14/2002	Renji Yang	0109015/024	4868

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EXAMINER	
HAYES, ROBERT CLINTON	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 01/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/047,352	YANG ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,23-25 and 28-80* is/are pending in the application.

4a) Of the above claim(s) *28-30,36-38 and 78-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,23-25,31-35 and 39-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *6,23-25 and 28-80* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed on 10/21/05 has been entered

2. Newly submitted claims 78-80 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Differentiated neurons are a separate and distinct population of cells, versus the originally elected neural precursor/stem cells.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 78-80 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

This application contains claims 28-30, 36-38 & 78-80 drawn to an invention nonelected with traverse in Paper No. 11/01/04. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. The rejection of claim 6 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn due to the amendment of the claim.

4. Applicant's arguments filed 10/21/05 have been fully considered but they are not deemed to be persuasive.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 6, 23-25, 31-35, & 39-77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In contrast to Applicants' assertions on page 12 of the response, no proper antecedent basis or conception exists on pages 5, 10 or 19 for the broader concepts now claimed. For example, no proper antecedent basis or conception exists in context with that described within the specification at the time of filing the instant application for the following recitations:

"wherein *at least about 20 % of the cell line* is capable of differentiating into neurons upon *withdrawal of mitogen*". In contrast, page 18-19 alternatively contemplates "[a]pproximately 20-30% of the total [MycER-enhanced human CNS stem] cells expressed the mature markers of neurons...", in which differentiation into neurons is contemplated here using only MycER-enhanced cells; and not for any broader recitations of "receptor ligand-regulated c-myc gene" (e.g., as recited in claims 6, 23, 31, 51), nor for any generic "nuclear receptor" (i.e., as it relates to claims 48, 51 & 64), nor for "a c-myc *protein fused* with at least one nuclear receptor" (e.g., as it relates to claim 64), nor for "upon withdrawal of [any structurally undefined] mitogens" without also withdrawal of *B*-estradiol (e.g., see pg 18), versus withdrawing only the specific "mitogens" contemplated and described, for example, in original

claim 31; thereby, constituting new matter for the new and broader scope now recited in the claims.

No proper antecedent basis or conception is apparent in context with that described within the specification at the time of filing the instant application for the broader recitations of "wherein the c-myc construct *includes at least a portion of* a c-myc *DNA* (versus the c-myc cDNA)... encoding *at least a portion of"* a ligand binding domain", and for the recitations of wherein the second mitogen is no longer "other than the first mitogen", and for any "c-myc-activating agent", versus the previously recited Markush group (i.e., as it all relates to claims 31, 51, 64, 71 & 77). Likewise, no proper antecedent basis or conception is apparent in context with that described within the specification for using any generic "proto-oncogene", or any other proto-oncogene construct, except for mycer construct used to establish the solely described cell line within the instant specification (i.e., as it relates to claim 72); thereby, constituting new matter.

Additionally, no proper antecedent basis or conception is apparent in context with that described within the specification at the time of filing the instant application for the broader recitations of "differentiate into... *glial"* (i.e., as it relates to claim 34), "wherein the culture includes a *monolayer* (versus feeder) component" (i.e., as it relates to claims 39, 57 & 68), "tissue selected from the group consisting of ... *diencephalon, mesencephalon...*" (i.e., as it relates to claims 42, 56, 67 & 76), "wherein the neural precursor cell is derived from an *adult* human" (i.e., as it relates to claim 53), "further comprising culturing the neural precursor cells in the presence of *unmodified* cells..." (i.e., as it relates to claims 62 & 63) , "a neural precursor cell line... capable of *expanding through at least thirty cell doublings* and wherein *at least 20%* of

the cell line is capable of differentiating into neurons" (i.e., as it relates to claim 64), "wherein the neural precursor cell line *includes a neural stem cell line*" (i.e., as it relates to claim 65) , and for "includes a *clonal cell culture*" (i.e., as it relates to claims 44, 46 & 73); thereby, also constituting new matter.

Lastly, no written description of any "c-myc *gene*" with its structurally definable 5'- and 3'-flanking regions, or for any "portions thereof", or for any "proto-oncogene", or for any "other DNA elements" have been described within the instant specification. See MPEP 2163.

Note that the claimed invention must be fully supported by the specification as filed. In contrast, Applicants' specification fails to provide *ibsis verbis* support for the now claimed invention, in contrast to their assertions on page 12 of the response. Nor does Applicants provide arguments reciting page and line number that implicitly or explicitly support the newly claimed invention; especially as it relates to new claims 39-80. In other words, it is strongly suggested that Applicants claim the invention actually described within the originally filed specification.

7. Claims 6, 23, 25, 31 & 33-35, 39-51 & 54-77 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakafuka et al (IDS Ref #26), for the reasons made of record in Paper No: 20050124, and as follows.

In contrast to Applicants' as arguments on page 13 of the response, the 12% of Nakafuka's cells that differentiate into neurons occurs only under conditions where "both β-E2 and bFGF" are present (pg. 162, 2nd col), which appears similar to that disclosed on page 18 of the instant specification, and therefore, does not exclude Nakafuka's cells from being "**capable of** differentiating into neurons upon withdrawal of [any] mitogen" including bFGF if they chose

to do such. Thus, Applicants' arguments are not on point with that currently claimed (i.e., a cell culture **product**) or with what Nakafuka et al actually teach; especially when Nakafuka et al teach *in vitro* stable cultures of rat/mammalian neural precursor cells with the same *mycer* construct as used in the instant application, which is also claimed, in contrast to Applicants' assertions on page 13 of the response. Moreover, in difference to Applicants' arguments concerning whether or not Nakafuka "culture the neural precursor cells in a serum-free medium...", if a claimed product in a product-by-process claim (i.e., a "cell culture *comprising* a neural precursor cell line...) is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process. *In re Thorpe.,* 227 USPQ 964, 966 (Fed. Cir. 1985): *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983). In addition, it has been established by the courts that a product (i.e., the claimed neural precursor cell cultures) inherently possesses characteristics of that product (i.e., neural precursor stem cells), and that:

"the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Accordingly, since the issue in the present appeal is whether the prior art factor is identified or patently indistinct from that of the material on appeal, appellants have the burden of showing that inherency is not involved". *Ex parte Gray,* 10 USPQ 2d 1922 (1989); *In re Best,* 195 USPQ 430 (CCPA 1976).

Lastly, it is noted that the courts have held that when the prior art product reasonably appears to be the same as that claimed, but differs by process in which it is produced, a rejection of this nature is eminently fair and the burden is upon the appellants to prove, by comparative evidence, a patentable difference (*In re Brown*, 173 USPQ 685 (1972)).

In summary, Nakafuka et al teach *in vitro* stable monolayer and suspension clonal cultures of rat/mammalian neural precursor cells (which are at least initially cultured in the presence of unmodified cells/incomplete transfections) using the same *mycer* construct as used in the instant application (i.e., c-myc proto-oncogene cDNA construct fused to the ligand binding domain of an estrogen receptor selectable marker; pgs. 155, 156, 162 & Table 1; as it relates to claims 6, 23, 31, 39, 43-46, 48-49, 51, 57, 59, 62-64 & 68-69); thereby, establishing the clonal cell line, MNS-57. These MNS-57 cells maintain a multipotential capacity to differentiate into neurons, astrocytes and oligodendrocytes/glial (e.g., pgs.153, 154, 159-160 & especially162 (2nd col.); as it relates to claims 23, 25 & 34-35). It is noted that the method of producing these cells using various mitogens, such as bFGF or EGF or β-E_2 (e.g., pgs 155-156 & 157-162) does not change the inherent properties of these claimed precursor/stem cell **products** (i.e., as it relates to claims 6, 31, 40, 51, 58, 60, 64 & 70-71); especially when CNS neural stem cells are inherently and naturally derived from pluripotent embryonic stem cells (i.e., as it relates to claims 25 & 33), and structurally and functionally possess the same inherent properties no matter what region within the brain from which they are derived (i.e., as it relates to claims 25, 33, 41-42, 50, 53-56 & 65-67); absence evidence to the contrary.

8. Claims 6, 23-25, 31-35, & 39-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakafuka et al (IDS Ref #26), in view of Eilers et al (IDS Ref #20) and/or Evans et al (1988), for the reasons made of record In Paper No: 20050124, and as follows.

In contrast to Applicants' arguments on pages 13-15 of the response, as discussed above in *pp* #7, Applicants' arguments are not on point with the pending rejection, or with the "product" claimed, and therefore, are not persuasive for the reasons made of record.

In summary, Nakafuka et al. is as described above. However, although Nakafuka et al. teach the importance of "understand[ing] the developmental processes of the [mammalian/ human] CNS" (pg. 153), they do not specifically teach a stable culture of human neural precursor cells.

Eilers et al. teach both the c-myc construct used above by Nakafuka et al., as well as a similar c-myc construct, *mycgr*, contains the sequence that encodes the hormone [ligand] - binding domain of the rat glucocorticoid receptor fused to the 3' end of *myc* transforms these cells in a glucocorticoid-dependent manner (pg. 67, 1st *pp*; as it relates to other ligand binding domains in claims 23, 31, 43, 48, 49, 51, 59, 64, 69 & 72). However, although Eilers use a human myc construct, they do not specifically teach a stable culture of human neural progenitor cells.

Evans is a review describing the well known ligand binding domains of steroid/thyroid hormone receptors (e.g., pg. 891; as it relates to estrogen, androgen, progesterone, glucocorticoid, thyroid hormone, retinoid and ecdysone receptors and their respective ligands/myc-activating chemicals in claims 23, 31, 43, 48, 49, 51, 59, 64, 69, 70 & 72). However, Evans does not teach stable cultures of human neural progenitor cells transfected with a c-myc construct.

It would have been obvious to one of ordinary skill in the art to produce stable mammalian/human neural precursor cells, as taught by Nakafuka et al., using any well known

steroid/thyroid hormone receptor ligand binding domain, as taught by Evans, fused to Eilers' c-myc constructs, because Eilers et al teach that "similar chimaeras" transform cells in a steroid/ thyroid hormone-dependent manner, and because of the potential human neural stem cells specifically possess in treating neurological disease states by replacing neural tissue that no longer exists, and by eliminating/minimizing host immuno-rejection of neural stem cells from non-human species.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for this Group is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert C. Hayes, Ph.D.
January 3, 2006

ROBERT C. HAYES, PH.D.
Primary PATENT EXAMINER